REMARKS

Claims 173-194, 196-203, 205-211, and 231 are currently pending. Claims 182 and 200 have been amended. The amendments to claims 182 and 200 do not constitute new matter.

The Examiner has provisionally rejected claims 173-194, 196-203, 205-211 and 231 under the doctrine of obviousness-type double patenting as unpatentable over claims 153-173 of copending Application No. 10/729,056. The Examiner has also rejected claims 173-194, 196-203, 205-211, and 231 under the doctrine of obviousness-type double patenting over claim 8 of U.S. Patent No. 6,410,587.

The Examiner has rejected claims 173-181, 205-211, and 231 under 35 U.S.C. § 103(a) as obvious over Sawada *et al.* (Pharmacometrics, 1992, 44(4):357-373). The Examiner has rejected claims 182-194, 196-203, 205, and 206 under 35 U.S.C. § 103(a) as obvious over Warri (Dissertation Abstracts International, 1993). For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

Double Patenting Rejections

The Examiner has provisionally rejected claims 173-194, 196-203, 205-211 and 231 under the doctrine of obviousness-type double patenting as unpatentable over claims 153-173 of copending Application No. 10/729,056. As noted in the previous response filed February 13, 2006, Applicants will consider the submission of a terminal disclaimer upon notification of allowable subject matter in U.S. Application No. 10/729,056 or the present application.

The Examiner has also rejected claims 173-194, 196-203, 205-211, and 231 under the doctrine of obviousness-type double patenting over claim 8 of U.S. Patent No. 6,410,587. Applicants will consider the submission of a terminal disclaimer upon notification of allowable subject matter in the present application.

The Claims Are Not Obvious

The Examiner has rejected claims 173-181, 205-211, and 231 under 35 U.S.C. § 103(a) as obvious over Sawada *et al.* (Pharmacometrics, 1992, 44(4):357-373) ("Sawada"). The Examiner states that it would have been obvious to modify Sawada to reach the present invention

> "because Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats. One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis.... That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol)."

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

Applicants respectfully disagree with the Examiner, and submit that there is no suggestion or motivation to modify Sawada to reach the present invention, because Sawada teaches against the use of higher doses of toremifene. Applicants would like to draw the Examiner's attention to the following passage of Sawada:

> In a 13-week toxicity study performed earlier, 0.007, 0.07, 0.7, 7 and 70 mg/ml were administered orally to female rats. The 0.07 mg/ml group experienced suppressed weight gain, and the 0.7 mg/ml group and higher groups experienced suppressed weight gain, a total cholesterol reduction, and atrophy and diminution of the uterus. These toxic changes such as suppressed weight gain suggested that 1 mg/ml should be the high dose, and that a maximum dose of 10 mg/ml would likely result in significant toxic changes. 0.1 and 0.01 mg/ml were thus set as the middle dose and minimum dose, respectively.

See Sawada at page 3, paragraph [08] (emphasis added).

Applicants submit that there is insufficient suggestion or motivation to modify Sawada to reach the present invention. Sawada discloses that suppressed weight gain and total cholesterol reduction occur together, and characterizes these features as "toxic changes." *Id.* Sawada also discloses that the changes coincide with a drop in overall feed consumption. See Sawada at page 8, paragraph [22]. Sawada is teaching that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada also links decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada at page 13, paragraph [43]. Sawada is therefore teaching against the use of such dosages, due to the associated toxicity. In addition, Sawada fails to teach, suggest, or imply that toremifene is or could be a therapeutic anti-cholesterol agent. Rather, Sawada is teaching that if toremifene is administered in a dosage where a decrease in total cholesterol is observed, that dosage is toxic, and a decrease in feed consumption is also observed. Based upon the disclosure of Sawada, it is unclear whether the reduction in total cholesterol is due to the

action of toremifene on TGFβ levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. Accordingly, because of the toxic effects of toremifene, and because the cause of total cholesterol reduction is unclear, Sawada does not provide the suggestion or motivation to reach the present invention.

The Examiner has rejected claims 182-194, 196-203, 205, and 206 under 35 U.S.C. § 103(a) as obvious over Warri (Dissertation Abstracts International, 1993) ("Warri"). The Examiner states that it would have been obvious to modify Warri to reach the present invention because "[o]ne would have been motivated to increase the level of TGF-beta by employing toremifene in order to achieve an expected benefit of treating breast cancer in mammal in any population including the patients having any other multiple disorders including diabetes, retinopathy."

Applicants note that claims 182 and 200 have been amended to recite "administering to a mammal at risk of or afflicted with said cardiovascular or vascular indication." Support for these amendments can be found in the specification at, for example, page 4, lines 3-8. Applicants submit that there is insufficient suggestion or motivation to modify Warri to reach the present claims, as amended. Warri discloses that, in breast cancer cells, toremifene increases TGFβ1 and promotes apoptosis. See Warri at page 51 ("TGFβ1 mRNA levels were enhanced only after higher concentrations of toremifene, and not after E2- withdrawal."). However, the conclusions of Warri are specific to breast cancer cells. Warri does not have the suggestion or motivation for a person of ordinary skill in the art to extrapolate the results for breast cancer cells found in Warri to other, non-breast cancer cells. Similarly, a person of ordinary skill in the art would not have a reasonable expectation of success in utilizing toremifene to treat cardiovascular indications, because there is no teaching that toremifene would have the same TGFβ1 increasing

effect in cells other than breast cancer cells. Applicants note that the reference concurrently submitted with this response, Sato, does not provide any teachings regarding the effect of toremifene upon non-breast cancer cell lines, and does not provide the teachings missing from Warri. Accordingly, because the conclusions of Warri are specific to breast cancer, a skilled artisan would not have sufficient suggestion or motivation to reach the present invention, and would not have a reasonable expectation of success of treating a cardiovascular indication with toremifene.

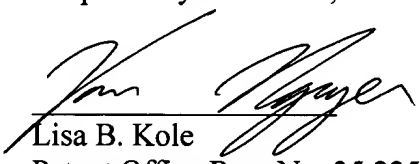
Applicants submit that Warri does not teach all of the elements of the present invention, because Warri does not disclose the use of toremifene to treat retinopathy or diabetes as recited in claims 183-185, nor does Warri does disclose the administration of toremifene to a mammal at risk of or afflicted with a cardiovascular or vascular indication. While the Examiner states that it would have been obvious to utilize toremifene to treat retinopathy or diabetes because Warri teaches the use of toremifene to treat breast cancer, this is insufficient to show a *prima facie* case of obviousness. See MPEP § 2143.01 ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.... A statement that modification of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all of the aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.") (emphasis in original). Accordingly, because the Examiner has not provided an objective reason to modify Warri with regard to retinopathy and diabetes, Warri does not teach all of the limitations of the present invention.

Based upon the foregoing, Applicants assert that the present invention is not obvious in view of Sawada or Warri, and respectfully request withdrawal of the rejections.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that the inventions described and defined by claims 173-194, 196-203, 205-211, and 231 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,



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